throughout the specification and in pending claim 38. Support for new claim 61 is found throughout the specification, for example on page 12, lines 28-32; page 16, lines 18-22; page 17, lines 4-6; Example 4; in original claims 1 & 3, and in pending claims 32, 41 & 47. Support for new claim 62 is found throughout the specification and in pending claim 35. Support for new claim 63 is found throughout the specification and in pending claims 42-43. Support for new claim 64 is found throughout the specification, for example on page 10, lines 32-33. Support for new claims 65-66 is found throughout the specification, for example on page 17, lines 20-34; page 19, line 14 to page 23, line 30. Support for new claim 67 is found throughout the specification and in pending claim 39. Support for new claim 68 is found throughout the specification and in pending claim 40.

Cancellation and/or amendment of the claims should in no way be considered to be an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the subject matter of the invention. Applicants reserve the right to pursue claims as originally filed in this or a separate application(s).

Attached hereto is a marked up version of the changes made to the claims by the current amendment with additions underlined and deletions bracketed. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Examiner Interview

Applicants wish to thank the Examiner for the courtesy of granting an interview to Applicants' representative on April 25, 2001 during which interview the pending rejections were discussed. Applicants acknowledge with appreciation the Examiner's helpful suggestion of claims language, which is reflected in the claims put forth in the present Amendment.

Claim Objections

Claims 35, 44 and 50 were objected to. Claims 35, 44 and 50 have now been cancelled, thus the objection is obviated.

Rejection under 35 U.S.C. § 112, first paragraph – written description

Claims 33, 34, 43, 44, 49 and 50 were rejected under 35 U.S.C. § 112, first paragraph, in view of the Office's determination that the specification fails to provide an adequate written

description. Applicants respectfully traverse this rejection to the extent that it may be deemed to pertain to new claims 52-55 and dependent claims thereof, for the following reasons.

It is the Examiner's position that the specification fails to demonstrate that "the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants respectfully disagree. The claimed invention is directed to expression vectors that comprise a nucleotide sequence encoding a fusion protein comprising an immunoglobulin heavy or light chain and an antigenic polypeptide. Claims 52-55 set forth that the polypeptide is either a mammalian antigenic polypeptide, an autoantigenic polypeptide or an antigenic polypeptide of an allergen comprising at least two epitopes. For reasons described in detail below, Applicants were in possession of the claimed invention at the time the application was filed.

First, the nucleotide sequences encoding such antigenic polypeptides were available in the art at the time the application was filed. Applicants refer the Examiner to Exhibit A, enclosed herewith, which presents a summary table and copies of the Genbank records listed in the table. These records are representative examples of nucleotide sequences available in the art prior to the 1994 priority date of the instant invention, corresponding to pollens (e.g., rye grass and Kentucky blue grass), ragweed allergens (e.g., Amb a I.1 and Amb a I.2), dust mite allergens (e.g., Der pI and Der fII), human coagulation factor VIII, human acetylcholine receptor (muscarinic receptor HM4), human collagen Type I, human myelin basic protein, human thyroglobulin and human histocompatibility antigens (MHC antigens HLA-DR, -DQ and -DP). Applicants emphasize that these sequences are merely representative examples of such sequences available in the art prior to 1994 and that numerous other sequences of the claimed antigenic polypeptides were readily available to the ordinarily skilled artisan at the time of the invention. Thus, the instant situation is clearly different from the fact pattern of the *Eli Lilly* case cited by the Examiner, in which the applicants were claiming a previously unknown nucleotide sequence and yet the specification failed to disclose the nucleotide sequence.

Second, the specification describes in detail how to use the claimed expression vectors encoding the fusion proteins comprising the antigenic polypeptides. For example, the specification teaches that a nucleotide sequence encoding an entire antigenic polypeptide can be inserted into the fusion protein. That is, the specification teaches that it is not necessary to select *a priori* a particular subregion of the antigen to include in the fusion protein. Applicants refer

the Examiner to the specification at page 11, lines 11-34, which describes the selection process for the epitopes. The specification states, for example, that

> if tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined in a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin [lines 16-20]. . . . [I]f there is little or no information known about epitopes of the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin [lines 30-34].

Finally, subsequent to the filing of the instant application, Applicants have conducted additional experiments according to the teachings of the specification using full-length antigenic polypeptides incorporated into the fusion protein. These experiments involved analysis of four full-length antigens, including myelin basic protein, and are described in detail below with regard to the lack of enablement rejection and in the accompanying Declaration under 37 C.F.R. 1.132 by David W. Scott. These experiments demonstrate that incorporation of a full-length antigen into the fusion protein induces tolerance to the antigen in a mammalian host. That is, as taught by the specification, use of the nucleotide sequence encoding the antigen in the fusion protein leads to a construct that induces tolerance to the antigen in a host individual (*i.e.*, it is not necessary to select a subregion of the antigen as the tolerogenic epitope to be included in the fusion protein).

In view of the foregoing, Applicants were in possession of the claimed invention at the time the application was filed and the specification meets the written description requirement. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph – enablement

Claims 33, 34, 43, 44, 49 and 50 were rejected under 35 U.S.C. § 112, first paragraph in view of the Office's determination that the claims are not supported by an enabling disclosure. Applicants respectfully traverse this rejection to the extent that it may be deemed to pertain to new claims 52-55 and dependent claims thereof, for the following reasons.

New claims 52-55 are directed to expression vectors that comprise a nucleotide sequence encoding a fusion protein comprising an immunoglobulin heavy or light chain and an antigenic polypeptide. Claims 52-55 set forth that the polypeptide is either a mammalian antigenic

polypeptide, an autoantigenic polypeptide or an antigenic polypeptide of an allergen comprising at least two epitopes. To satisfy the enablement requirement, the specification must provide sufficient guidance regarding how to make and use the invention to allow the ordinarily skilled artisan to carry out the invention without undue experimentation. For reasons discussed in detail below, the instant specification meets the enablement requirement.

The specification describes how to prepare expression cassettes for the fusion proteins (e.g., pages 8-17). The specification further describes how to transform cells with the expression cassettes (e.g., pages 17-19). With regard to the particular antigenic polypeptides recited in claims 62-64, the specification describes that the nucleotide sequences for these antigens are available in the art and can be identified by searching in a database such as GenBank (e.g., page 10, lines 5-20). Applicants again refer the Examiner to the summary table of Exhibit A, and the GenBank entries described therein (discussed in detail above with regard to the lack of written description rejection), which demonstrates that nucleotide sequences of these antigenic polypeptides were available in the art at the time the application was filed. Furthermore, the specification describes how to select epitopes of the antigens, if desired, for inclusion in the fusion protein. Applicants again refer the Examiner in particular to the specification at page 11, lines 11-34, which describes the selection process for the epitopes. The specification states, for example, that

> if tolerance is desired to a large and complex antigen, more than one epitope can be selected to be combined in a fusion immunoglobulin. Preferably, the entire antigen may be included in the fusion immunoglobulin [lines 16-20]. . . . [I]f there is little or no information known about epitopes of the antigen, it may be desirable to include the entire antigen in the fusion immunoglobulin [lines 30-34].

Subsequent to the filing of the instant application, Applicants have conducted additional experiments according to the teachings of the specification using a variety of different antigenic polypeptides incorporated into the fusion protein. These experiments and their results are discussed in detail in the accompanying Declaration under 37 C.F.R. 1.132 by David W. Scott. Briefly, in addition to the experiments described in the Examples section of the specification (at pages 31-43), Applicants have constructed six additional different fusion proteins and tested their ability to induce tolerance in a host individual. Four of these fusion constructs used full-length

proteins as the antigenic polypeptide incorporated into the fusion protein. The four full-length polypeptides tested were: myelin basic protein (MBP), glutamic acid decarboxylase (GAD), lambda repressor cI protein and ovalbumin (OVA). Two other fusion constructs used subregions of antigenic polypeptides, wherein these subregions were established in the art to elicit an autoimmune response in an appropriate host . These two additional constructs tested were: interreceptor retinal binding protein (IRBP) residues 161-180 and insulin B chain residues 9-23.

As described in the Declaration, all six of these expression (fusion) constructs induced tolerance to the antigenic polypeptides (or portion thereof) incorporated into the fusion protein in a host individual. These results demonstrate that incorporation of a full-length antigenic polypeptide or a portion thereof into a fusion protein in accordance with the teachings of the specification is sufficient to induce tolerance to a wide variety of different antigens. Thus, the teachings in the specification are sufficient to teach one of ordinary skill in the art to create fusion protein constructs for antigenic polypeptides such as those set forth in claims 62-64, and that these fusion protein constructs would be capable of inducing tolerance. In view of the specification, this does not require undue experimentation.

With regard to the Examiner's allegation that the term "autoantigens" is not defined in the specification and does not have an art recognized meaning, Applicants respectfully submit that the term does in fact have a meaning that is well known in the art. For example, Stedman's Medical Dictionary (26th Edition) defines the term as "any tissue constituent that evokes an immune response to the host's tissues." As illustrated in Janeway et al., *Immunobiology*, pages 489-509, 4th ed., autoantigens are self-antigens associated with auto-immune diseases in which individuals develop autoantibodies to self-antigens. Illustrative examples of autoantigens are also provided in the specification, for example at page 10, lines 25-28.

With regard to the Examiner's statement that pollen, ragweed and dust mites are made up of more than just protein and thus it was unclear what Applicants intended to claim, Applicants note that new claim 63 is directed to a protein of pollen, a protein of ragweed and a protein of dust mite. Thus, the Examiner's concern is obviated.

For the foregoing reasons, the instant specification meets the enablement requirement. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 31-51 were rejected under 35 U.S.C. § 112, second paragraph in view of the Office's determination that the claims are indefinite for failing to point out and distinctly claim the subject matter that Applicants regard as the invention.

The Office has determined that a number of terms render the claims indefinite. Applicants traverse this ground of rejection, however, in the interests of expediting the prosecution of this application, Applicants have addressed the Examiner's concern regarding the terms and phrases "functional", "said fusion immunoglobulin", "derived", "to which tolerance is to be induced", "associated with", "the heavy chain" and "characteristics" by incorporating into the new claims language that more clearly point out what Applicants regard as the invention.

With respect to the Examiner's assertion that claims 34, 43 and 49 are indefinite because it is unclear whether Applicants intend to claim antigens derived from proteins within the organisms or antigens derived from a non-protein which causes an immune response which is found within the organisms, Applicants note that new claim 63 recites a protein of pollen, a protein of ragweed and a protein of dust mite.

With respect to the Examiner's allegation that the term "autoantigen" in claims 35, 44 and 50 are indefinite because an antigen that is recognized as a "self-antigen" in one person may not be recognized as "self-antigen" in a different person, and that the term "histocompatibility antigen" is also indefinite, Applicants disagree. As described above, the term "autoantigen" has an art-established meaning. In the context of an autoantigen, the meaning of the term "histocompatibility antigen" would also be known to the person of skill in the art, and thus is not indefinite.

Applicants do not, by this amendment (cancellation of pending claims and addition of new claims), surrender any subject matter. Applicants have not altered the scope of the subject matter as claimed, but more particularly point out what is claimed. It is Applicants' position that, in view of the specification, the language of the new claims is clear and definite.

Rejection under 35 U.S.C. § 102(b)

Claims 31, 32, 37, 39 and 40 were rejected under 35 U.S.C. § 102(b) as being anticipated by Zambidis *et al.* Applicants respectfully traverse this rejection to the extent that it may be deemed to pertain to new claims 52-55, and dependent claims thereof, for the following reasons.

For a cited reference to anticipate a claimed invention, the reference must disclose each and every element of the claimed invention. The claimed invention is directed to expression vectors that comprise a nucleotide sequence encoding a fusion protein comprising an immunoglobulin heavy or light chain and an antigenic polypeptide. Claims 52-55 set forth that the polypeptide is either a mammalian antigenic polypeptide, an autoantigenic polypeptide or an antigenic polypeptide of an allergen comprising at least two epitopes. None of these is disclosed in Zambidis et al. The Zambidis et al. reference describes a fusion protein construct composed of a mouse IgG1 and the immunodominant epitope 12-26 from bacteriophage lambda cI repressor protein. Zambidis et al. do not teach a fusion protein construct comprising a mammalian polypeptide, nor an autoantigenic polypeptide, nor an antigenic polypeptide of an allergen comprising at least two epitopes.

Since the Zambidis et al. reference does not disclose all the limitations of the claimed invention, it does not anticipate the present claims and Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 31-33, 36, 37, 39-42, 45-48 and 51 were rejected under 35 U.S.C. § 103(a) as being rendered obvious and unpatentable over Zambidis *et al.* taken in view of Zanetti *et al.* and Chambers *et al.*

Applicants respectfully traverse this rejection to the extent it may be deemed to apply to new claims 52-55, and dependent claims thereof, for the following reasons.

As discussed under the §102 rejection above, Zambidis et al. does not teach all the limitations of the claimed invention. Chambers and Zanetti do not cure this deficiency. The Chambers reference is directed to expressing lymphokines in peripheral blood lymphocytes (PBL) using a retroviral construct encoding the b-actin promoter/enhancer, and the Zanetti reference is directed to construction of immunoglobulin molecules that are able to localize on certain cell/receptor sites and elicit reactivity to antigens specific for an introduced novel antigenic determinant or epitope. Neither of them teach a mammalian antigenic polypeptide, an autoantigenic polypeptide or an antigenic polypeptide of an allergen comprising at least two epitopes.

Furthermore, Applicants respectfully submit that there is no motivation to modify the construct disclosed in Zambidis et al. or combine the cited references. The Zambidis abstract reports preliminary work of the present inventors describing only a specific exploratory vector. Although the abstract generally discusses that the purpose of making the immunoglobulin fusion protein therein was to attempt to induce tolerance, the abstract does not provide any teachings of tolerance induction but only the invitation to experiment. It was the subsequent experiments performed and reported in the instant application which led to the invention wherein compositions and methods of achieving tolerance could be described. The Zambidis reference does not teach how to use a fusion immunoglobulin molecule for induction and maintenance of tolerance. It merely makes such experiments obvious to try and further does not provide a teaching of how to go about it. Thus, there was no reasonable expectation of success in achieving tolerance induction in view of the teachings of the Zambidis reference. Without such a reasonable expectation of success, the expression vectors claimed herein would have no utility and thus there would be no incentive to make them or, more importantly with regard to the obviousness rejection, no motivation or suggestion to modify the vector of Zambidis et al. or to combine the teaching of Zambidis et al. with Chambers et al. or Zanetti et al.

The Examiner relies upon one of the secondary references, Chambers, as providing the requisite motivation for making the claimed invention, in particular "because the retroviral vector of Chambers is an improved method of transfecting reproducing cells such a lymphoid or hemopoietic cells" and that "[o]ne of ordinary skill in the art would have recognized the ability to improve transduction in lymphoid cells using the retroviral vector and to express the fusion protein in lymphoid cells to study the immune system which was common at the time of filing." The retroviral vector constructs of Chambers, however, encode lymphokines, which have a demonstrated function and utility in the immune system and thus there is a clear reason to express such lymphokines in lymphoid cells. In contrast, the fusion immunoglobulin of Zambidis et al. has no demonstrated function or utility. Absent such a teaching in Zambidis et al., at the time the invention was made there would have been no motivation for the ordinarily skilled artisan to modify the teachings of Zambidis et al. by combining them with the teachings of Chambers et al. to create a retroviral vector construct.

The Examiner cites Zanetti et al. as supporting the expression of proteins in T-cells and PBL and the Examiner's position that one of ordinary skill would have a reasonable expectation

of success in obtaining the claimed vectors and cells. Applicants note that the Zanetti et al. reference merely noted that the constructs disclosed therein can be used for immunizing against pathogens, and hypothesizes that it can be used to build tolerance to antigens. Zanetti, however, does not provide any teachings of tolerance induction. Indeed, the primary focus of the reference is the use of the constructs for *inducing* an immunogenic response, as illustrated in the extensive teachings and data on this point. It is notable that the example provided is an immunodominant epitope of the malarial plasmodium falciparum circumsporozoite, an epitope to which one would not want to induce tolerance. Moreover, since the Zambidis construct has no demonstrated function or utility, there would have been no motivation for the person of skill in the art to modify the teachings of Zambidis et al. by combining them with the teachings of Zanetti et al. to achieve the claimed invention.

For the foregoing reasons, the claimed invention is nonobvious over Zambidis *et al.* taken in view of Zanetti *et al.* and Chambers *et al.* Accordingly, Applicants respectfully request that this section 103 rejection be reconsidered and withdrawn.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 308072000110. However,

the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 21, 2001

Respectfully submitted,

By: _____

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Limited Recognition Under 37 CFR §10.9(b)
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

New claims 52-68 have been added.

EXHIBIT A

Table 1

PubMed Accession No.	Allergen/Autoantigen	Source Organism	Nucleic Acid	GenBank Record No.	Published
M59163	Rye grass pollen	*Lolium perrene*	mRNA	gi:485370	1991
M38342	Kentucky blue grass pollen	*Poa pratensis*	mRNA	gi:169626	1991
M62981	Ragweed Amb a I.2 (antigen E)	*Ambrosia artemisiifolia*	mRNA	gi:166436	1991
M63116	Ragweed Amb a I.1 (antigen E)	*Ambrosia artemisiifolia*	mRNA	gi:166433	1991
M24794	Dust Mite[1] Der p1	*Dermatophagoides pteronyssinus*	mRNA	gi:387591	1988
D10448	Dust Mite Der f II	*Dermatophagoides farinae*	mRNA	gi:217305	1991
K01740	Coagulation factor VIII:C	*Homo sapiens*	mRNA	gi:182802	1984
X15266	Acetylcholine Receptor (muscarinic acetylcholine receptor HM4)	*Homo sapiens*	DNA	gi: 32323	1987
X55525	Collagen Type I	*Homo sapiens*	mRNA	gi:30101	1990
M30047	Myelin Basic Protein	*Homo sapiens*	mRNA	gi:187400	1986
X05615	Thyroglobulin	*Homo sapiens*	mRNA	gi: 37173	1987
M11867	Histocompatibility antigen HLA DR5 beta chain	*Homo sapiens*	mRNA	gi:188229	1986
M24364	Histocompatibility antigen HLA DQ beta chain	*Homo sapiens*	mRNA	gi:529041	1989
M28200	Histocompatibility antigen HLA DP beta chain	*Homo sapiens*	mRNA	gi:575493	1989

[1] Also, see: Hoyne et al., *Immunology* 1993 Jan; 78(1):65-73; which teaches the immunological responsiveness of mice having differing major histocompatibility congenic strains to specified peptides representing the dust mite epitope of allergen Der p II